Biological Methods.—Hypertension was induced in male Sprague-Dawley strain rats, weighing approximately 200 g, by the bilateral carotid cannulation method of Abrams and Sobin.\(^{10}\) Antihypertensive activity of the test compounds following single subcutaneous medication was estimated in unanesthetized and hypertensive rats in terms of AED\(_0\) values. The AED\(_0\) is defined as the approximate dose of the test compound, expressed in mg/kg, found to reduce the systolic blood pressure to a normotensive level in 50% of the animals tested. Systolic blood pressure was measured indirectly by means of the photoelectric, telemeter system method of Kerven, et al.,\(^{10}\) utilizing three hypertensive rats per dose level. Systolic blood pressure of 130 mm Hg or less was considered normotensive. Blood pressure was measured before and at 1, 2, 4, 6, 24, and 48 hr following medication.

Compounds were administered once daily in gelatin capsules for 5 non-consecutive days a week at each dosage level to unanesthetized hypertensive rats. The methods for the induction of hypertension in dogs and the medication test procedure were described previously.\(^{11}\)

Groups of four female Sprague-Dawley strain rats were used for the tissue catecholamine depletion studies. At least two groups were used for each medication level with duplicate assays on each group. Medications to 40 mg/kg were given subcutaneously 4–6 hr prior to sacrifice. After decapitation, hearts were immediately frozen over alcohol-Dry Ice. The frozen tissues were weighed and homogenized in 0.4 N HClO\(_4\) and assayed by a modified alumina absorption procedure of Anton and Sayre.\(^{12}\) Estimates were based on the ethyleneileamine-stabilized trihydroxynaphthyl procedure of von Euler and Lishajko.\(^{13}\) The AED\(_0\) was defined as the dose expressed as mg/kg of base producing a 50% reduction in tissue catecholamine content. AED\(_0\) values were estimated graphically.

Acute toxicity was expressed in terms of the approximate LD\(_50\). AED\(_0\), by intravenous injection into male, Webster strain, albino mice weighing 22 ± 2 g. The compounds in aqueous solution were injected into groups of three mice each of three or more dose levels.

Amphetamine Analogs. II.

Methylylated Phenethylamines\(^{1}\)

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In our previous work on amphetamine analogs,\(^2\) 2,5-dimethoxy-4-methylamphetamine (DOM, 1) was found to decrease the pentobarbital-induced sleeping time in mice. It exerted an effect nearly as pronounced as amphetamine.\(^2\) Since the stimulating effect of methamphetamine is known to be more pronounced than its nonmethylated analog,\(^1\) it would be interesting to find out if the introduction of a methyl group on the nitrogen of DOM (see 2) would potentiate its effect both on the sleeping time and the disruption of animal behavior. The effect of mesanine (3) on the behavior of rats has also been reported.\(^4\) Interest in what the activity would be when the aminopropyl side chain of 1 is replaced by an aminomethyl linkage led us to synthesize 2,5-dimethoxy-4-methylphenethylamine (4) as well as its N-methylated derivatives 5 and 6.

Condensation of the 2,5-dimethoxy-\(\rho\)-tolualdehyde with nitromethane gave the \(\beta\)-nitrostyrene which was then reduced by LiAIH\(_4\) to 4. By a reductive formylation method, 4 was converted to its N,N-dimethyl analog 6. The N-methyl compounds 2 and 5 were prepared by the methylation of Schiff's bases formed from benzdihydraldehyde and the corresponding amine.

The results of the conditioned behavioral (VI) tests are expressed as E\(_{50}\) (Table 1). Compounds which were the most active in disrupting rat behavior were DOM (1) and 4. Although 4 had three-fourths of活性 of 1, it is five times more potent than 3. N-Methylation of both the phenylisopropylamine and the phenethylamine series resulted in compounds much less effective in behavioral disruption. A fivefold loss in activity was observed from 1 to 2, and a 7.5-fold loss from 4 to 5. However, no further decrease in activity was noted when a second methyl group was introduced to 6.

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose (mg/kg)</th>
<th>Mouse sleeping time (min)</th>
<th>Dose (mg/kg)</th>
<th>Rat E(_{50}) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 ± 4</td>
<td>31.0 ± 1.4</td>
<td>&lt;0.001</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>110 ± 3</td>
<td>40.5 ± 6.4</td>
<td>NS(^{2})</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>80 ± 1.3</td>
<td>98.5 ± 8.5</td>
<td>&lt;0.001</td>
<td>7.2</td>
</tr>
<tr>
<td>4</td>
<td>85 ± 4.1</td>
<td>46.4 ± 2.7</td>
<td>&lt;0.10</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>100 ± 1.6</td>
<td>35.5 ± 1.2</td>
<td>NS</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>315 ± 20.5</td>
<td>34.4 ± 2.1</td>
<td>&lt;0.01</td>
<td>38</td>
</tr>
</tbody>
</table>

\(^{2}\)Dose required for 50% decrease in conditioned response. \(^{3}\) Data from ref. 2. \(^{4}\) p value larger than 0.10 was considered to be not significant (NS).

The effects of 1 and 3 in decreasing the pentobarbital sleeping time have previously been reported.\(^{2}\) In this study, among the four compounds 2, 4, 5, and 6, both 4 and 5 were found to potentiate the sleeping time. It is interesting to compare the structures of 3 and 4 and to note that two opposite effects on the sleeping time resulted as the substituents on the benzene ring were varied. It remains to be determined if 3 and 4 have any effect on the metabolism of pentobarbital that could vary the sleeping time. As great as a fourfold difference in toxicity was also observed between 3 and 4 (Table 1).

\(^{1}\) This work was supported by Grant MI-12990, U. S. PHS Health Service, Bethesda, Md., and by the Britton Fund.


Experimental Section

2.5-Dimethoxy-4-methyl-α-nitrostyrene.—A mixture of 5.5 g (30 mmoles) of 2,5-dimethoxy-4-toluic aldehyde, 2.5 g of 
NH2OH, 25 ml of CH3NO2, and 25 ml of C6H6 was refluxed for 20 
hr, during which time H2O was azeotroped with a Dean-Stark 
tube. After cooling, the resulting solution was washed success-
ively with H2O (two 25-ml portions), saturated solution of 
NaHCO3 (two 25-ml portions), and H2O (two 25-ml portions). 
The C6H6 layer was dried (Na2SO4) and evaporated in vacuo, 
leaving 6.0 g (92%) of yellow solid, mp 111-112°C. Recrystal-
ization from C6H6-C6H14 (1:2) gave 5.3 g (79%), mp 118-119°C. 
This melting point remained unchanged upon another recrystal-
lation. Anal. C12H9NO2 C, H, N.

2,5-Dimethoxy-4-methyl-β-phenylethylamine (4).—To a 
stirred suspension of 2.0 g (80 mmoles) of LiAlH4 in 30 ml of 
THF was added a solution of 4.4 g (18 mmoles) of 2,5-dimethoxy-
4-methyl-α-nitrostyrene in 50 ml of THF. The mixture was 
refluxed for 1 hr, cooled in ice, and treated with a mixture of 
H2O and THF to decompose excess LiAlH4. The resulting mix-
ture was filtered and the filter cake was extracted with THF. 

The free amine was precipitated with Et2O-HCl, a hydrochloride salt precipitated, yield, bp 79° (0.075 mm) to 
82° (0.05 mm), mp 150-151°C. Recrystallization from EtOH gave 4.4 g (60%), mp 150-151°C. Anal. C13H15ClNO C, H, N.

2,5-Dimethoxy-N,N4-trimethyl-α-phenylethylamine (5).—A mixture of 5.8 g (30 mmoles) of 2,5-dimethoxy-4-methyl-α-
phenylethylamine (4), 4.2 g (40 mmoles) of benzaldehyde, and 15 
ml of C6H6 was refluxed for 30 min and then subjected to distilla-
tion until the temperature reached 100°C. To the remaining viscous 
liquid was added dropwise a solution of 5.4 g (40 mmoles) of H2SO4 
in 20 ml of C6H6. The mixture was first heated until the reaction 
was complete, then 3.6 g (0.12 mole) of formalin in 10-ml portions. 
The mixture was treated with Et2O-HCl, a hydrochloride salt 
precipitated, mp 168-169°C. Recrystallization from EtOH gave 
1.5210. When a solution of this product in Et2O was mixed 
with C6H6 (three 5-ml portions), the C6H6 layer was dried 
(370°C) and evaporated in vacuo, leaving 3.7 g of oily product. 
A solution of this oil in 25 ml of EtOH was treated with EtOH-HCl 
to precipitate 4.1 g (83%) of the hydrochloride salt, mp 200-203°C. Recrystallization from EtOH gave 1.8 g, mp 212-213°C. 
Addition of EtOH to the filtrate yielded 3.4 g (83% of the 
total yield was 62%). Anal. C12H14N C, H, N.

In a separate run distillation of free amine yielded 59% of a 
iliquid, bp 95-105° (0.15 mm), nD20 1.5385.

2.5-Dimethoxy-N,N4,4-trimethyl-β-phenylethylamine (6).—To 14.0 
g (0.82 mole) of formic acid, cooled in ice-H2O, was added 
dropping-wise 10 g (0.66 mole) of 2,5-dimethoxy-4-methylphenyle-
thymine (4), then 3.6 g (0.12 mole) of pyridine in 10-ml portions. 
The mixture was refluxed for 5 hr. After cooling to room tem-
perature, 7 ml of concentrated HCl was added and the resulting 
solution was evaporated in vacuo leaving 3.7 g of oily product. 
A solution of this oil in C6H6 was refluxed for 30 min. Next, 20 ml of water 
was added and refluxing was continued for an additional 30 min. 

The aqueous phase was separated, extracted with CHCl3 (two 25-
ml portions), made basic with 2N NaOH, and again extracted 
with C6H6 (three 25-ml portions). The combined C6H6 extracts 
were dried (Na2SO4) and evaporated in vacuo. Distillation of the 
residue gave 4.0 g (79%) of product, bp 96-99° (0.075 mm), 
nD20 1.5278. When a solution of this product in 30 ml of EtOH was 
treated with EtOH-HCl, a hydrochloride salt precipitated, yield 
3.3 g (83%), mp 130-131°C. Recrystallization from EtOH gave 2.5 g (60%), mp 150-151°C. Anal. C15H21NO C H, N. 

2,5-Dimethoxy-N,4-dimethyl-β-phenylethylamine (2).—The procedure was the same as described for the preparation of 
2,5-dimethoxy-N,4-dimethyl-α-phenylethylamine (5). The free amine was obtained in 65% yield, bp 79° (0.075 mm) to 82° (0.05 mm), 
nD20 1.5240. When a solution of this product in 50 ml of EtOH was mixed 
with EtOH-HCl, the hydrochloride salt separated as an oil at first 
and then solidified; yield 60%, mp 122-123°C. For purification, 
the hydrochloride salt was dissolved in a small amount of EtOH 
and slowly precipitated with Et2O. In this fashion pure 2, 
mp 121-122°C, was obtained in 46% yield. Anal. C13H14NO C, 
H, N.

(5) Melting points were taken in a Mel-Temp apparatus and are cor-
rected. Where analyses are indicated only by symbols of the elements or 
functions, analytical results obtained for those elements or functions 
were within ±0.4% of the theoretical values.